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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,552	09/22/2003	Johannes Bartholomaeus	029310.50777CP	6176

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EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
09/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,552	BARTHOLOMAEUS ET AL.	
	Examiner	Art Unit	
	S. Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/13/09 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an oral dosage form of tramadol and diclofenac, does not reasonably provide enablement for the specific release profiles recited in claims 27 and 28. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: breadth of the claims, nature of the invention, state of the prior art, amount of direction provided by the inventor, the level of predictability in the art, the

existence of working examples, quantity of experimentation needed to make or use the invention based on the content of the disclosure, and relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors being discussed below:

Breadth of the claims is broad. Independent claim 1 is directed to an oral formulation comprising combination of tramadol and diclofenac in separate subunits. Dependent claims 27 and 28 require specific release profiles from the dosage form of claim 1.

Amount of direction provided by the inventor, and quantity of experimentation needed to make or use the invention: independent claim 1 does not recite any structure of the dosage form that specifically leads to the claimed release profiles. Much less, the claims broadly recite just an oral dosage form. There are quite a large number of dosage forms out there that are suitable for oral administration. A review of the present specification shows that different dosage forms with different structures result in different release profiles (see examples 1-4). Further, the present specification does not teach how to precisely achieve the claimed release patterns or profiles given the multitudes of types of suitable dosage forms with multitudes types of coating polymers. The specification also fails to teach if different release profiles can be achieved from the same dosage form as recited in claim 1. The specification does not provide any guidance as to how one can achieve different types of release rates with the same amount of drug in a dosage form. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

As such, the practitioner would turn to trial and error experimentation in order to compose the claimed oral release dosage form of tramadol and diclofenac without guidance from the specification or the prior art.

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Claim Rejections - 35 USC § 103

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. US 4,690,927, in view of On US 6,319,514 or Raffa EP 0 546 676 A1, and Addicks et al. US 5,041,430, and Bergamini et al. US 5,597,560 or Bodley et al. US 5,679,660.

Voss teaches a pharmaceutical dosage form comprising mixture of diclofenac sodium and salt of codeine in a weight ratio of about 1:1 to 3:1 (abstract; and claims 1-3). The dosage is suitable for oral administration in the form of granule, dragee, tablet, layered tablet, and capsule (column 2, lines 11-64). The two active substances can be formulated in separate layers in a tablet (ID). The final dosage form can be film coated with hydroxypropylmethyl cellulose (example 1).

Voss is only deficient in the sense that Voss does not teach the use of tramadol.

On teaches a narcotic analgesic includes codeine phosphate, tramadol hydrochloride, and related analogues having similar analgesic property (column 3, lines 4-9).

Raffa teaches tramadol and it's salt such as tramadol hydrochloride is an "atypical" opioid analgesic, a very unique drug that when combine with an NSAID, will exhibit superadditive analgesia (page 2, lines 20-21; and page 3, lines 5-7).

Thus, it would have been obvious to one of ordinary skill in the art to optimize the combination of Voss to include the use of tramadol to obtain the claimed invention. This is because Raffa teaches a preferred selection of tramadol over codeine to reduce side effects associated with opioid analgesics (page 2, lines 4-28), because On teaches the equivalency or at least similar analgesic properties between codeine and tramadol (ID)., and because Voss teaches the desirability of combining diclofenac with an opioid analgesic compound to achieve a more intense therapeutic effect but eliminating side effects (column 2, lines 5-10).

Voss further does not explicitly teach the separation of two active agents.

Addicks teaches a dosage form comprising combination of at least two active agents, wherein the active agents are separated by a coating layer to minimize physical contact between the active agents to prevent chemical interaction (columns 4-5). Thus, it would have been obvious to one of ordinary skill in the art to include the separating layer between the diclofenac and the codeine to obtain a more stable composition. This is because Addicks teaches a dosage form suitable for the delivery of at least two active agents that are known to have potential for chemical interaction (column 3, lines 65 through column 4), and because diclofenac is known in the art to exhibit interaction with quite a number of active agents. See for example Bergamini et al. at column 7, lines 20-30; and Bodley et al.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raffa US 5,516,803, in view of Voss et al. US 4,690,927 and Addicks et al. US 5,041,430 and, and Bergamini et al. US 5,597,560 or Bodley et al. US 5,679,660.

Raffa teaches a composition comprising combination of tramadol and an NSAID (abstract; and column 3, lines 15-59). NSAID includes diclofenac (column 4, lines 29-37).

It is noted that Raffa teaches diclofenac among a number of NSAID. However, it would have been obvious to one of ordinary skill in the art to modify the teachings of Raffa to combine tramadol with the well known NSAID such as diclofenac, because Raffa suggests NSAID includes diclofenac.

However, to be more specific, Voss is cited for the teachings that a combination of diclofenac sodium with an analgesic drug will increase desired analgesic effect (column 1, lines 5 through column 2). The active substances can be formulated in separate layers in a tablet (ID). The final dosage form can be film coated with hydroxypropylmethyl cellulose (example 1).

Thus, it would have been obvious to one of ordinary skill in the art to modify the composition of Raffa to combine tramadol and diclofenac. This is because Raffa teaches the desirability to obtain an analgesic composition with less opioid side-effects, and because Voss teaches an analgesic composition with minimum side reactions.

Raffa does not teach the separation of two active agents.

Addicks teaches a dosage form comprising combination of at least two active agents, wherein the active agents are separated by a coating layer to minimize physical

contact between the active agents to prevent chemical interaction (columns 4-5). Thus, it would have been obvious to one of ordinary skill in the art to include the separating layer between the combination of active agents such as tramadol and diclofenac to obtain a more stable composition. This is because Addicks teaches dosage forms suitable for the delivery of at least two active agents that are known to have potential for chemical interaction (column 3, lines 65 through column 4), and because diclofenac is known in the art to exhibit interaction with quite a number of active agents. See for example Bergamini et al. at column 7, lines 20-30; and Bodley et al.

Response to Arguments

Applicant's arguments filed 05/13/09 have been fully considered but they are not persuasive.

Applicant's arguments with respect to the 112, first paragraph rejection that the experimentation would not be undue, is not persuasive for the following reasons:

1) although the examples disclosed the dosage structure of the claimed invention, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993);

2) the specification discloses different dosage forms with delayed release profiles;

3) the present specification discloses quite a number of water-insoluble polymers that can be used as a coating or matrix base for the dosage forms; and

4) from the broadest limitation of the present claim 1, the claim does not define any structure of the "oral administration unit" in the sense that would enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Let alone, the present specification discloses quite a number of dosage form that could be selected as an oral administration unit, such as microtablets, microcapules, ion-exchange resinates, granules, crystals or pellets. The unit can be coated with a retard coating comprising multitude type of polymers (paragraphs 0020-0022), such as water-insoluble polymers, water-soluble polymers, and waxes. The unit may further comprise additional coating, and/or matrix materials (paragraphs 0022-0024). With quite a number of different dosage structures, and multitude type of materials that can be incorporated in the dosage unit, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. This is also evident by the disclosure of the examples in the present specification that, different dosage structure will result in a different release profile (see examples 1-4). As such, the practitioner would turn to trial and error experimentation in order to compose the claimed oral release dosage form of tramadol and diclofenac without guidance from the specification or the prior art.

Accordingly, the 112, 1st paragraph rejection of claims 27 and 28 are maintained.

Applicant argues that the deficiencies in the cited references, taken as cited by the Office, have been discussed previously. There is nothing in any of the cited art, as combined by the Office, which even hints at these unexpected benefits. Even if a

showing of obviousness is believed to have been presented, it is overcome by the unexpected beneficial results achieved in accordance with the invention of the present claims. The present invention relates to the discovery that tramadol (hydrochloride) and diclofenac (sodium) form a sparingly soluble compound. That is, when formulated together, these ingredients form a compound with a relatively low solubility. This low solubility is undesirable where there is a need to ensure that the active ingredients are released from the formulation within a short time following administration. By providing these active ingredients in separate subunits no such sparingly soluble compound is formed and the active ingredients may be release more quickly than if the active ingredients were simply mixed together. Thus, providing the active ingredients in separate subunits provides an unexpected and unforeseen beneficial effect, namely that the release of the active ingredients can proceed much faster than if the ingredients were mixed together during the formulation process. In particular, in certain embodiments the invention allows the skilled artisan to achieve a release rate of tramadol (hydrochloride) and diclofenac (sodium) from a common administration unit which matches the release rate from administration units having only tramadol (hydrochloride) or diclofenac (sodium) as the active ingredient, see, e.g. paragraph [0048] of the present application and Figures 1, 3 and 4.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

However, it is of note that the art recognizes the need to separate drugs that are known to exhibit chemical interactions when formulate together in a single dosage form.

Applicant's attention is called to the teachings in Addicks at columns 4-5, where Addicks teaches a dosage form comprising combination of at least two active agents, wherein the active agents are separated by a coating layer to minimize physical contact between the active agents to prevent chemical interaction. See also Bergamini et al. and Bodley et al. for the teachings of diclofenac as a drug that is known to have chemical interaction when formulated with other drugs.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1615